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STORAGE

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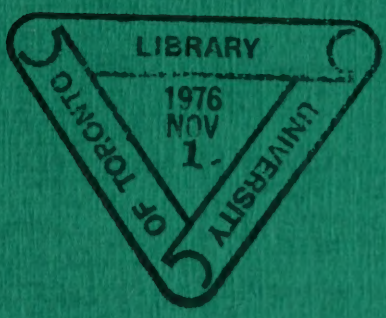

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TRANSACTIONS

OF THE

SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

APRIL, 1911.

VOLUME IV. No. 6.

Proceedings of a Meeting of the Society on Friday, March 17th, 1911.

SIR HAVELOCK CHARLES, K.C.V.O., in the Chair.

THE SPECIFIC CURE OF YAWS BY DIOXYDIAMIDO-ARSENOBENZOL.*

BY

RICHARD P. STRONG, M.D.,

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A few months ago, through the kindness of Professor EHRLICH, I received a shipment of dioxydiamidoarsenobenzol for use for experimental purposes in syphilis. I take great pleasure in acknowledging here publicly my thanks to him for the opportunity to try the effect of this very valuable preparation. On account of the favourable results which were being obtained with it in the treatment of syphilis, the idea naturally suggested itself to try the remedy in yaws, on account of the morphological and biological relationship which exists between the spirochætæ giving rise to these two diseases.

Yaws is a disease which is not only highly disfiguring, but is very contagious, and usually runs a chronic course, frequently preventing the

* Preliminary remarks on this subject were made before the Manila Medical Society on September 5th, 1910, where photographs and one of the cured patients were presented.

patient from attending to his work, and sometimes eventually disabling him. The treatment has hitherto been most unsatisfactory, and usually a prolonged one is necessary before success is obtained. While, among the better classes afflicted, cures after long periods have frequently resulted, as a rule the disease is one of very long duration and yields but slowly to medication. Even the patients who can be seen in the dispensary and hospital usually become discouraged with the treatment long before a cure results, and often abandon it. In the cases among the lower classes of people, the successful treatment of this disease has hitherto been entirely impracticable, both for the reason that it has usually been impossible to persuade and to cause individuals to undertake a prolonged course of treatment, which, to be ultimately successful, frequently must be pursued for many months.

From the articles of MANSON, SCHEUBE, CASTELLANI, PLEHN, FIRTH, and JEANSELME, one is impressed with the very unsatisfactory status of the treatment of the disease at the present time. DANIELS, who has had a particularly wide personal experience in the treatment of yaws, writes :—

"Probably no drug influences the duration of the disease. Mercury and arsenic certainly do not. Potassium iodide is uncertain in its action. The eruption will sometimes disappear rapidly when iodides are given, but even in such cases when the use of the *drug is continued* fresh eruptions appear. The use of iodide is therefore limited. Local applications that merely serve to keep the granuloma clean are valuable, but escharotics and irritants, though they may destroy the yaws, are likely to cause the formation of scars. The painful granulomata on the feet are best destroyed by the action of nitric acid, acid nitrate of mercury of silver nitrate."

It is not my intention here to enter into a prolonged discussion of the question of the specificity of yaws as a disease. Almost all observers agree that yaws is not identical with syphilis. SCHEUBE and FIRTH are inclined to support the original idea of HUTCHINSON that yaws was the original disease from which European syphilis has been evolved, or that the two diseases developed from a parent form, each having been modified by being propagated by different races in different climates. MANSON, CASTELLANI, JEANSELME and PLEHN regard the two diseases as specifically distinct.

The inoculation experiments in man and animals performed by CHARLOUIS, NEISSER, BAERMANN, HALBERSTADTER, CASTELLANI, ASHBURN and CRAIG, LEVADITI, and others, also confirm the idea that the two diseases are etiologically distinct.

Up to the present time I have treated thirty cases of yaws with dioxydiamidoarsenobenzol. A report of the cure of three of the most striking cases was made before the Manila Medical Society on September 5th, where photographs and one of the cured patients were exhibited. The report of all of the cases has been withheld until the present time, in order to ascertain if relapses would occur in any of them. So far there has been no evidence of a relapse, and the cases have all remained cured, although the majority of them were treated over six months ago.

The preparation was received in hermetically sealed capsules. The capsules were opened and the solution always prepared immediately before being inoculated. The preparation as EHRLICH has stated is not readily soluble, and in order to obtain a satisfactory solution his suggestions were followed. From 0·3 to 0·4 gram of the preparation was placed in a glass vessel, moistened with a few drops of methyl alcohol, and thoroughly rubbed up with a glass rod. From 20 to 30 cubic centimetres of distilled water were then added, the stirring with the glass rod being continued. When the solution was apparently completed, 5·5 cubic centimetres for 0·3 gram of the preparation of an N/10 sodium hydroxide solution was slowly added, stirring with the glass rod being continued and causing the precipitate, which forms on this addition, to slowly redissolve.

The injections were given deep into the gluteal muscle, from 15 to 20 cubic centimetres of fluid being usually injected in one place. On the following day after there was usually some reddening, swelling and induration of the skin and underlying tissues in the vicinity of the point of the inoculation. In no instance did suppuration result, and in no case did any unfavorable symptoms develop. Occasionally a transitory rise of temperature was noted a few days after the injection. In some of the instances, pain after the injection was complained of, sometimes lasting for from 10 to 24 hours, or sometimes even longer. However, usually following the inoculation no great complaint was made of pain. A number of the cases inoculated have been among young children who did not cry, neither during nor after the injection was given; usually they did not care to play for the first 24 hours following the injection. In one European suffering with tertiary lesions of syphilis, who was given a large injection into the buttock, severe pain lasting for nearly 24 hours was complained of. This case was given a second injection

intravenously twenty days later. No pain whatever followed this second injection.

For the cases of yaws treated it was found that in almost every instance a single injection of the drug was sufficient to produce a cure,* even though a number of the cases showed tertiary lesions with ulcerations. In none of the cases was any local treatment employed, or was any other treatment internal or otherwise administered after the injection. In the few cases that had been treated with iodides previously, these were discontinued a few days before the injection of dioxydiamidoarsenobenzol was given.

CONCLUSIONS.

Dioxydiamidoarsenobenzol appears to be an ideal specific for yaws. Three or four days after the injection of the drug, the granulomatous lesions begin to disappear, and in the course of from ten to twenty days they have usually entirely disappeared, leaving a perfectly smooth pigmented skin where the lesions previously existed. The absorption of tumor masses measuring several centimetres in diameter and about a centimetre in thickness in so short a time, and under the influence of no local treatment whatever, has been very striking and surprising. Indeed, in the severe cases, the disappearance of the lesions and the cures produced could be most aptly spoken of as marvellous. Even in cases where large granulomatous masses or deep ulcerations existed, these were healed within from two to four weeks. I do not know of any more striking example in medicine of a specific action than of that produced by dioxydiamidoarsenobenzol on the lesions of yaws.

A slight reddening appears about the margins of the lesions in from twenty-four to forty-eight hours after the injection of the preparation. The centre of the lesion then usually assumes a purplish or bluish congested appearance. Phagocytes are attracted to this area, which now assumes a greyish or brownish hue. The spirochætæ quickly disappear and the granulomatous tissue becomes absorbed, leaving dark pigmented areas of skin, which later resume their normal colour. In the cases where crusts have existed, these frequently are not absorbed, but drop off.

* Only two of the cases required a second injection.

As stated above, none of the cases have shown any signs of relapse, although all with the exception of two received but a single injection, and over six months have elapsed since most of the cases were inoculated.

Nevertheless, I believe that in a few of the most severe cases of the disease, where the ulcerations are extensive and of long-standing, a second inoculation, about three weeks after the first one, may be advisable. Only in No. IV. of the first series of yaws cases which I treated with this preparation was there any question as to whether a second dose should have been given, and as to whether a second one might not have hastened the cure. However, the lesions eventually entirely healed as a result of the primary dose.

The dose of the preparation for the treatment of yaws should be from 0·25 to 0·3 gram for children, and from 0·5 to 0·7 gram for adults. Small doses may not give such favourable results.

Some observers have claimed that it is not advisable to attempt to repress the eruption of yaws, as this may be accompanied by considerable constitutional disturbance. The employment of dioxydiamidoarsenobenzol simply caused the eruption to fade away. There were no unfavourable constitutional symptoms other than an occasional transitory rise of temperature produced thereby, and the patients seemed improved in health following the disappearance of the eruption. A number of authors have also laid great distress upon the local treatment of the disease. If dioxydiamidoarsenobenzol is employed, the local treatment, except in cases of severe ulcerations, and where other organisms than Treponema pertenuis have invaded the lesions, is entirely unnecessary. Case IV. would undoubtedly have been cured more quickly if the ulcerating granulomatous masses had been curetted and disinfected and dressed daily with sublimate solution, since other spirochætæ than spirochæta pertenuis, and bacilli, and cocci were present in the lesions. However, even in this case the lesions eventually entirely healed without local treatment.

The cure of yaws by this preparation, and the successful results which have been obtained with it in the treatment of certain cases of syphilis may suggest again the identity of yaws and syphilis. It does not appear strange that this preparation should have such a destructive action against both Treponema pertenuis and

Treponema pallidum, since both from a morphological and biological standpoint these two organisms appear closely related. Indeed, potassium iodide, which is so valuable in the treatment of syphilis, has hitherto been the most successful remedy employed in the treatment of yaws. As has been pointed out by other observers, the therapeutic argument for the identity of yaws and syphilis, and hence for the identity of their specific organisms, is very fallacious. Many instances in medicine might be quoted in support of this statement. Quinine which destroys certain forms of *Plasmodium malariæ*, *Plasmodium vivax*, and *Laverania malariæ*, also destroys *Amœba dysenteriæ*.

In conclusion, it would appear that dioxydiamidoarsenobenzol is as important a specific for yaws as quinine is for malaria, and hence a fourth medicinal specific in medicine has been discovered.

While these experiments in treatment were in progress, the articles of NICHOLS were published on the successful transmission of the spirochætæ of yaws to the rabbit's testicle ("Journ. Exp. Med.", Sept., 1910), and on the cure by injections with dioxydiamidoarsenobenzol of these experimentally produced lesions in four of these animals and in three monkeys moderately infected with yaws ("Journ. Am. Med. Assn." July 16, 1910).

DISCUSSION.

Dr. CARNEGIE BROWN: I should like to mention that with reference to the very remarkable advance in the treatment of yaws recorded in Dr. STRONG'S paper, an article on the same subject has recently been published in the "Archiv. für Schiffs und Tropen-Hygien" by Dr. CASTELLANI, which supplies very strong corroboration of the efficacy of dioxydiamidoarsenobenzol. No doubt most of you have seen that paper, but for the benefit of those whose attention it has escaped, I may say that a series of cases of yaws were treated in Ceylon, much in the same way as those in Manila by Dr. STRONG, by injections of "606," which had been sent to Dr. CASTELLANI by Professor EHRLICH—and that in almost every instance, the effect of a single injection was to induce a very remarkable amelioration in the condition of the patient. The improvement was specially marked in recent cases, but apparently the beneficial effects of the drug are by no means limited to the earlier stages of the disorder.

Dr. C. W. DANIELS: Judging from the photographs the treatment with "606" would appear to be very successful. Occasionally under potassium iodide in the past as rapid improvement takes place, but these cases have been rare and the recurrence of the disease has been almost invariable. The new treatment certainly looks most promising and I only hope that it will be possible to reduce the cost of the drug. It is also to be hoped that the drug will not have the effect some people say it has in syphilis, viz., that it so effectually eradicates the disease that there is no subsequent immunity; because if it destroys immunity I am not at all sure that the last state would not be worse than the first; for when adults contract the disease at a more advanced age it occurs in rather a serious form and is the cause of a good deal of inconvenience. Dr. CORNEY, who is present, is the authority on the subject of yaws and will no doubt give his opinions.

Dr. B. G. CORNEY: I am afraid, Mr. Chairman, I have very little to say about the matter as it is now some few years since I left the colony where yaws was prevalent; I quite agree, however, with my friend and former colleague, Dr. DANIELS, that the treatment we have heard described to-night does appear undoubtedly very promising. I do not wish to be pessimistic, but I think perhaps the claims made for the new treatment are a little premature as regards the tertiary conditions of yaws. Judging from my own knowledge of the course of the disease in South Sea Islanders, I think that in 15 years' time we may be able to say definitely whether this is a cure or not, but not at present. I have no doubt the treatment has relieved the cases just described in the paper, and to that extent it is likely to prove of great use, qualified by the very pertinent remarks and suggestions of Dr. DANIELS; but I certainly think a much longer period than a few months ought to elapse before we draw positive conclusions as to the efficiency of this drug as an eradicator of yaws from the system. It is a known fact for the disease to spontaneously disappear in many South Sea Islanders who have had yaws in childhood, and then, after an interval of from 15 to 18 years, for the tertiary conditions to arise. We shall therefore have to wait some time before we can say definitely that the administration of this drug is going to prevent the tertiary conditions altogether.

Mr. T. PUGH BEDDOES: These results are extremely favourable but with different technique similar results (possibly even more favourable) with distinctly less pain would be obtained if, instead of a solution of methyl alcohol and sodium hydroxide, an emulsion made in sterile olive oil is used, and if in place of injecting 30 to 35 c.c. only 6 c.c. were injected, that is, 3 c.c. into each buttock. This quantity could be injected into the patient in one operation and after one or two hours rest there is absolutely no pain. There is practically no pain at the time of the injection if a slightly soluble cocaine substance is used, such as orthoform, anæthesin or betaeucain, ½ grain to 6 c.c. of sterile oil. The only case treated in this way in which there was any pain, was that of a patient who, 48 hours after injection, took a fairly long walk and then had pain in the back. One patient who had been treated with calomel injections said that calomel was much more painful.

Fleet-Surgeon BASSETT-SMITH: There is just one point not touched upon in Dr. STRONG'S paper to which I should like to draw attention. Yaws is one of those diseases in which the Wassermann's Serum reaction test should be used before one can say whether the patient is cured or not. In syphilis, after the patient has been treated with "606" and has apparently been miraculously cured, the reaction yet remains positive for a long time, and until that reaction is proved negative, and continues negative, it is impossible to say that the patient is permanently cured. The same reasoning, therefore, should I think apply in regard to the treatment of yaws.

THE USE OF SANTONIN IN THE TREATMENT OF INTESTINAL AFFECTIONS OF THE TROPICS.

BY

J. PRESTON MAXWELL, M.D., F.R.C.S.

Our subject for to-night is:—"The use of Santonin in the treatment of intestinal affections of the Tropics," but I am deliberately excluding from our discussion its action as a vermifuge or vermicide.

Santonin (C_{15} H_{18} O_3) as you know, is a neutral crystalline principle extracted from the unexpanded flower heads of *Artemisia Maritima*. Probably, however, it is not truly neutral, but the anhydride of monobasic santonic acid, and its formula C_{15} H_{20} O_4.

Its general characteristics you all know, and I need not enter into them to-night. Suffice it to say that we have to deal with two substances, both of which pass under the name of Santonin.

The first is ordinary white santonin, which has been tried in the treatment of the affections which we are now discussing, and found to be useless or practically so.

The second is yellow santonin (Chromosantonin of Montemartini).* It is prepared by exposing ordinary santonin to prolonged sunlight, and that the yellow colour is not a mere colour change is proved by the following points.

"There is no change in weight, but the derivatives are different, the rotary powers are different, and the colour is different." If the yellow santonin be dissolved in alcohol, and repeatedly re-crystallized, it gradually passes back again into the white.

Chromosantonin is more readily oxidized, and the products of oxidization are said by MONTEMARTINI to be different. SESTINI† says that the white santonin is changed into formic acid, and an uncrystallisable substance much more soluble in alcohol and ether than santonin (photo santonic acid C_{15} H_{22} O_5) and a red resinous substance.

* Chromosantonin, Montemartini, 1902. Abstr. J.C.S. 1. 545.

† United States Dispensatory. 19th edition, page 1086.

Both the white and the yellow undergo oxidation in the tissues, and are excreted in the fæces and urine in several forms, two certainly oxysantonins (JAFFE).*

But little however is known of the process of oxidation. Under ordinary circumstances probably little is dissolved in the stomach. It may, however, in rare cases, be so rapidly absorbed as to be useless for the purpose of a vermifuge. The major part of the drug is absorbed from the intestine, and undoubtedly passes into the blood stream, as in large doses there is a marked influence on the cerebrum. It is certainly excreted by the kidneys, and possibly is re-excreted into the intestine. On the urinary passages it has some irritative action, and it may cause incontinence in children, and clinically in adults it may act as a diuretic, though CUSHNY† denies that there is any true diuretic action.

In large doses vision is markedly affected; first in the direction of bluish vision, followed by yellow vision, wherein everything white appears to be yellow; then there may be hallucinations of vision and confusion of speech, the sense of taste and smell may be deranged, and in rare instances, hearing likewise. As the effect of the drug passes off there may be a period of violet vision.

All these effects may supervene on a medicinal dose.

Poisonous doses do not concern us to-night, and it may be merely noted that there is a very marked cerebral disturbance in these cases.

The preparation of chromosantonin is not an easy matter. To get a really good specimen may need six months of sun in sub-tropical regions, and white santonin with a slight yellow tint is not chromosantonin, though it has, to my own knowledge, been used as such with consequent disappointment at the failure to get the expected result.

Let us now look for a few minutes at the history of the drug in this connection. Dr. CHARLES BEGG, whom we are all glad to see amongst us to-night, whilst in practice in Hankow, Central China, found by clinical experiment that santonin was a cure for certain forms of chronic tropical diarrhœa. He also found that the white variety was practically useless, and that the virtue of the drug lay in chromosantonin. He published the account of these cases in the "Reports of the Imperial Maritime Customs, 1887" (Shanghai, 1890, XXXIV.) Practically the

* Cushny. Pharmacology, 1906.

† Cushny. Pharmacology, 1906.

whole of the papers which advocate the use of this drug in this connection come from his pen.* For some unaccountable reason others have not been able to get the same results; and Sir PATRICK MANSON, in "Allbutt's System of Medicine, 1910," Vol. II., page 11, says:—"I have tried the method in a considerable number of cases, my experience has not been favourable." Dr. HARSTON, of Hong Kong, said to me at the last meeting of the British Medical Association, "What is the reason that many of our best men fail to get satisfactory results with yellow santonin?"—he himself having seen excellent results; and one hopes that a result of this evening's discussion will be to clear up this mystery. It is possible that the diseases which we discuss to-night are not entities, or that there is some unknown factor which may render a case amenable at one time and resistant at another.

It will now be my endeavour to set out before you a series of cases in which I personally have not a shadow of doubt that it acted as the curative agent. And in order to, as far as possible, eliminate the uncertainty which might attach to cases chosen at random, I have selected four cases, two male and two female, all personal friends of either the writer or his father (Dr. MAXWELL, late of Formosa), and in each case I have myself made the fullest enquiries. It will be noted that the ages of the patients vary greatly, and that the cases are drawn from Pekin, Foochow, Hong Kong, and Peru, a pretty wide range both as regards latitude and longitude.

(1). Take first the case of a lady. Miss D. arrived in the Fukien Province in January 1897, being then 28 years of age. Save for occasional attacks of malaria, she was well till August 1900 when she went home on furlough, her work having been closed owing to the Boxer rising. In the autumn of 1902 she returned to China, as far as she knew, in perfect health.

In April 1903 after a long and exhausting walk, she had an attack of nausea and diarrhœa. When that had passed, she was conscious that her appetite, which had not been over good for some time, was now nearly gone, she had a bad taste in the mouth, and she began to pass huge greyish stools. She was depressed and wretched.

* (*a*) *Edin. Medical Journal*, Sept., 1890, "Chronic Tropical Diarrhœa." (*b*) "Sprue and Spurious Dysentery," *Journal of the Royal Army Medical Corps*, July, 1905. (*c*) "Sprue," *Bristol Med. Chir. Journal*, June, 1905.

In August 1903 she went to Foochow and was put on milk by her doctor. She was much troubled by abdominal distension, and the treatment with powdered cuttle-fish bone was adopted without any benefit. She returned to her own station not much improved. In April 1904 she had a severe exacerbation, and soreness of the mouth began. She returned to Foochow where sprue was diagnosed, and she was sent up to the sanatorium at Kuliang, having a severe attack of tetany on the way.

In September 1904 she was decidedly worse, emaciated and depressed, and was sent home, leaving China in October 1904, it being supposed that the case was practically hopeless. The diagnosis was confirmed and she was carefully treated, being put on a milk diet. For two months she was up and down, getting gradually weaker, the mouth very sore and constant diarrhœa.

For six weeks after this, she was kept *in bed* on strict milk diet but still did not improve, and was so weak she could hardly stand.

In March 1905, on the advice of a friend, she decided to consult Dr. Begg, and being unable to travel, she wrote to him. She procured the medicine he recommended, namely yellow santonin, and took it in doses of five grains night and morning in olive oil for a week, keeping on with her milk diet.

At the end of that week, though still very feeble, she was a new woman; the colour of the stools had changed for the better and the frothiness had disappeared. She gradually left off invalid diet. Subsequently whenever she got chilled, she had small relapses. In May 1905 she was very much better, the final cure being hastened by iron and specially nourishing diet, and by the autumn she considered herself well.

She left again for her old station in August 1906 and in June 1910 I met her on her way home via Siberia for a three months' holiday. She was well, able to take any kind of food and not knocked up by any ordinary exertion.

She is now back again at her station in South China.

(2). Here is another lady. Miss H. returned to England from Hong Kong in August 1904 with "sprue" and very much run down in health. The diagnosis was confirmed in London and she was treated on the lines of the meat diet cure. This was kept up with slight alterations till May 1905, and it was thought that she was progressing favourably though

very slowly. In July 1905 she had a bad relapse and all the old symptoms returned. The diarrhœa was not severe, but she lost weight and the tongue was very sore. In September 1905 she consulted Dr. Begg and had a course of chromosantonin in olive oil, staying in bed for the week and keeping to her meat diet with a little milk pudding.

On the seventh day she was told to try ordinary diet and had bacon for breakfast, meat and blackberry and apple pudding for dinner, with no subsequent bad results. She never returned to invalid diet, though occasionally there was a little tendency to diarrhœa, began to put on weight and steadily progressed, but had occasional slight attacks of soreness of tongue. She is now well, but still subject to slight soreness of tongue if for any reason her stomach gets seriously upset.

(3). Take now the case of a gentleman, Mr. G. O., *æt* 68 at the present time. He went to China in 1865. In the year 1901 he began to have bowel trouble in Pekin. In the beginning of 1902 his tongue and throat became very sore, but he still felt fairly well. The stools were light, irregular, half solid, half fluid, and frothy.

He came to England in April 1902 and went steadily down hill, a wreck of his former self by the autumn, pale and weary and mouth very sore, stools about the same. He was under the care of several medical men and in the beginning of 1903 was in the London Temperance Hospital for six weeks, leaving it much the same.

In the early autumn of 1903 he was again treated in London, and was put on strict milk diet, and then on milk and bananas. He improved a little, but the mouth was still very sore, he was not fit for any work, and the slightest variation of diet brought on the symptoms as severely as before. He put on some flesh on 7 pints of milk a day and the bananas.

After 11 months of this diet, he was very much disheartened, and about June 1904 he consulted Dr. Begg. He had the usual course, preceded by castor oil and fearing lest he had not taken it thoroughly went on for 16 days.

He noticed first an immediate improvement in his general condition, feeling at the end of the course like a new man, and second that the stools had become altogether formed and had lost their frothy nature.

Fearing to damage the good effect he kept to milk and bananas for some time longer, and then gradually resumed ordinary diet. A short

time after he stopped the yellow santonin, he was alarmed by large pieces of mucus coming away with the stools but this rapidly ceased. The tongue began to improve at once under the yellow santonin, and was quite well in a comparatively short time. There has been no relapse of the mouth. On two occasions the bowels have been out of order and have promptly been put straight by a few doses of yellow santonin.

He now looks well and is in active work, though he does not think his old vigour has been regained ; a great portion of this however may be due to advancing age.

(4). The following is a somewhat different case. Mr. J. I. S., in the late fifties, acquired dysentery in Peru when 26 years old. He had several severe attacks. About 1906 he began to suffer again from it, passing at first a good deal of blood and mucus, and he was under treatment for about a year with the result that the blood ceased but the other symptoms did not improve much and he was an almost complete invalid. I quote from a letter of Dr. BLAKE of West Wycombe, under whose care he was at the time. "He was examined with the sigmoidoscope and as the sigmoid in his case had a mesenteric fold we were able to see well up and see the healthy bowel above the inflamed area which was covered with minute ulcers. We found a certain amount of benefit from a decoction of Simaruba and Cinnamon bark, but the yellow santonin was what cured the condition, in gr. V doses twice daily, the fœtor disappeared after two days, and the pain and tenesmus rapidly disappeared."

The patient told the writer that he was a new man at the end of the week, and that the sense of bien-être was very marked. The drug, which had been prepared by my father, (Dr. MAXWELL) in Bromley, Kent, was reduced after the first few doses to 2½ grains as the 5 grain doses were too strong for the patient. He has remained well since that date.

If the drug does what one claims for it, it should cure *(a)* early cases ; *(b)* relapses.

(a) Here is the story of an early case :—Miss S., a lady about 30 years of age came out to the Fukien Province, South China, in the spring of 1906. Within three months of her arrival she began to suffer from an early morning diarrhœa, sometimes having to go to stool two to

six times before 9 a.m., after which time she was free for the rest of the day. The stools were full of bile and there was much fermentation and flatus.

I tried, first, ordinary remedies including intestinal antiseptics, with the result that the patient was decidedly worse at the end of three weeks. I then put her on yellow santonin gr. V in olive oil twice daily, and she was well in a week and remained in the East without any further trouble of this kind for four years, when I had to invalid her home for a general breakdown due to unsuitable and exhausting work. She has just returned again to China. Here is another early case :—

Mrs. D., a lady of 33, was confined of her second child in May 1909. The puerperium was normal, but as soon as she began to get about again, she commenced to suffer from a sore mouth with swollen tongue, typical of the early stage of sprue, irregularity of the bowels and great depression. She was at once put on yellow santonin gr. V, twice a day, without the olive oil, and speedily recovered health, the mouth improving at once under the treatment. She had no return of the sore mouth, and went home on furlough in June 1910, in good health, having been 6½ years in the East and expecting to return to China next year.

In neither of these cases was there any restriction placed on the diet, save that in the first case the patient was carefully dieted during the *unsuccessful* three weeks treatment with ordinary remedies.

(b). Let us look now at relapses :—Mrs. E. M., *æt* 35 at the time of her illness, was invalided home in February 1903 from Amoy, South China, with a serious attack of sprue. Under a course of treatment with meat and milk diets, the disease was gradually overcome and she recovered a measure of health. In October 1904 she returned with her husband (the writer) to China. At this time there were many slight attacks of sore tongue and mouth, and marked tendency to diarrhœa. One day a week she spent in bed. Later on she took a course of yellow santonin which undoubtedly materially aided her ultimate recovery. The slight relapses gradually became fewer, though after the birth of a child at term in 1908 there was a distinct attempt at a serious relapse, promptly checked by castor oil and yellow santonin. She is now in perfect health, able to eat any food with impunity, to go out freely, and may be considered cured. I believe that had she been treated with *yellow* santonin in the earlier stages, the duration of the disease would

have been much shortened. Before leaving China she had been on milk diet and was treated with cuttle-fish bone without benefit.

The writer has never met with a typical case of sprue amongst the Chinese, but has tried the drug pretty extensively in cases of chronic dysentery. Some cases have been cured, and these were cases which were *not* amœbic in nature, and the cause was unknown. Cases where the round worm is the cause of course yield to this drug, but this class of case is not under discussion.

What is the action of the drug on the bowel? Clinically the frothy fermenting stools lose their frothy appearance, lose their fœtid odour or the peculiar "faint" odour, almost like that of a dead body, found in some cases, and become more solid and of a better colour.

Experiments have been lately undertaken with a view to elucidating the manner of action of the drug, but as yet nothing has emerged to explain such results as I have described.

CONCLUSIONS.

1. There are two substances known as santonin: Santonin and Chromosantonin. The last-named differs completely from santonin as regards its chemical composition, and therefore may be expected to show differences in its physiological action.

2. This chromosantonin exerts a marked influence on the development of putrefaction in the bowel.

3. It has a specific influence in certain cases at present classified under the wide term "Sprue," and in certain cases of chronic dysentery which are not due to the action of the amœba coli.

4. The differing reports as to its action are in part due to its not having been properly prepared, and it is important that in future work care should be given to this point.

I would close by saying that chromosantonin is not to be regarded as a cure-all. Nothing will *cure* a case of sprue or dysentery where there has been destruction of any large area of the intestinal mucous membrane, nor will any drug ensure a patient against possible relapse. On the other hand it deserves a careful trial in the treatment of intestinal affections, and one hopes that as a result of our discussion to-night this will take place.

The Chairman (Sir HAVELOCK CHARLES): I think we all owe our our thanks to Dr. MAXWELL for his very interesting paper. The fact that has most impressed me is that all his cases have been cures. This is marvellous in sprue, and the writer certainly seems to have been more fortunate than others. The discussion, which will be enlightening, will no doubt clear up many points raised by the paper. I will ask Dr. BEGG to open the discussion.

Dr. CHAS. BEGG: I have listened to Dr. MAXWELL'S paper with very great interest. My experience with santonin dates back more than thirty years, and has been gained partly in the East and partly in England. Elsewhere I have related how I found out its value. I had treated unsuccessfully several cases of chronic diarrhœa, when a pamphlet came into my hands describing such cases under the name of Sprue. The symptoms were well described, but the pathology was obviously faulty; it spoke of a primary atrophy of the mucous membrane from mouth to anus. That caused me to take up a study of these cases with renewed interest, and struck with the red irritable condition of the tongue, I began with santonin to eliminate the chance of the disease being caused by lumbrici or a similar parasite. Close watch was kept, but nothing of that nature was ever passed. Yet the motions rapidly improved, all the symptoms yielded, and the patients were cured. I treated enough patients to feel no doubt of this and then argued out an explanation: cure by santonin meant to me the killing of something with life, and if that something were not macroscopic it must be microscopic, and in an invasion by micro-organisms I felt I had the answer to the problem, and in santonin a drug that could kill them.

I published my results in 1887 in the "Medical Reports of the Chinese Imperial Maritime Customs," and in 1890, after more experience, I came home, and then got into touch with several chronic cases from India—two in particular that were well-known to the leading specialists in London. The drug acted as completely as before. I then read a paper before the Edinburgh Medical Chirurgical Society, which was published in the September number of the *Edinburgh Medical Journal* of that year. Immediately after that, the first post-mortem ever held in a sprue case, took place. Dr. WETHERED kindly went over his slides with me, and I had

the satisfaction of finding my explanation of the cause of the disease confirmed, and it is the generally accepted explanation to-day. I then returned to the East and am able to say that during the rest of my stay there I never failed to cure every case that occurred in my practice, or that came to me from other parts of China. The picture is different during the experience I am now having at home. The only comparatively recent cases I get to treat are those who come direct to me from abroad. The majority are cases of long standing—cases that have tried all the so-called cures (diet is not a cure, although it may be a help to the organism to cure itself). This is not a discussion on sprue, and the time given me is limited, so I must only indicate, as shortly as possible, the experience that places me in a position to express an opinion as to the value of santonin in intestinal disease. In the East I was treating only the sprue seen in China, now I have to deal with the Ceylon sore mouth, the Indian hill diarrhœa, the sprue of Burma, Straits Settlements and elsewhere, cases from the Congo, one case from Morocco, cases that had developed in England after a life spent in perfect health in the tropics, a case where there was a perfect clinical picture of sprue, and yet the patient had never been in the tropics. A certain proportion of these cases were cured, some extremely rapidly. With many I failed, but that cannot be wondered at, as they were long past the stage at which a cure could be hoped for, either on account of the great destruction of the mucous membrane, or because of the complications that had appeared. I read a paper on these complications at the annual meeting of the B.M.A. in 1905, pointing out the importance of examining for and dealing with these complications. So much for sprue. Dysentery, and what I have called spurious dysentery, I have seen a great deal of, both in the East and in England, and santonin gave such splendid results in these cases that in 1905 I coupled dysentery with sprue in a paper I was asked to write for the journal of the Army Medical Corps. Since that date, two observers have recorded their experiences with the drug in dysentery. In 1907, Dr. Drake, of Assam, during an epidemic, treated every alternate case with santonin and the others in the usual way. *In Estate A*, the number of days to effect a cure by santonin was 6·58, and the deaths were 3; under the other the days were 13·1, and the deaths 13. *In Estate B*, where he notes the type of case during the experiment was especially bad, the number of

days under treatment by santonin was 9, with no deaths; under other treatment the number of days was 30, with 2 deaths. In 1908, Dr. BRUNWIN, Fiji, although he cannot give as startling statistics, reports fewer deaths and quicker recoveries, and states that he is so satisfied with his results that he will continue to use it in preference to any other treatment. Such has been my experience, and it has led me to endorse every one of Dr. MAXWELL'S conclusions, chromosantonin has a greater power than that possessed by any other drug in clearing up all cases that depend on the invasion of the intestine by micro-organisms. It has taught me the value of early administration, and has led me to make a habit of giving it in all cases of intestinal disease in addition to any other treatment that may be indicated. Time will not permit of my bringing before you details of cases in support of these conclusions, and they would be similar to those related by Dr. MAXWELL. I must proceed to the important point of the kind of drug and its administration. Dr. MAXWELL has spoken of the failure of others to obtain my results. It is simply because they have worked with the wrong drug—santonin instead of chromosantonin. It was unfortunate that just at the time I made my discovery, chemists had taken up the subject of the purity of drugs. Amongst others the action of light on santonin was held to cause a deterioration, and it was protected. I had been working with santonin that had been exposed to the sunshine of China for fourteen years; when that was finished my next supply came as white crystals. I found it perfectly useless. After experiment, I found that the value depended directly on the extent of the so-called deterioration. The formation of chromosantonin must be slow, and the process goes on indefinitely; a mere light lemon colour is not enough, and Dr. MAXWELL'S estimate of the time taken before it should be used is a fair one. Two weeks' exposure in India I have found to equal that of many months in England. That there is a change is certain. Observers in England have told me that the white drug no longer kills the lumbrici stone dead as does the yellow, and times out of number I proved that chromosantonin can do what the white drug cannot. To get the best results it must be given in oil, this may either be olive, almond, or, in certain cases, even castor oil. Gelatine capsules may be used; keratine coated ones have been spoken of. I must caution against their use in sprue when the acid secretions would most probably prevent the liberation of the drug.

A test for the necessity to administrate this drug is the loss of the normal alkalinity of the motions. Dr. MAXWELL has expressed the hope that this discussion may throw light on why my results are not obtained generally. I think the reasons are two: First, the proper drug has not been given; as an example, I remember talking to a well-known London specialist, who is now dead, who expressed his surprise that although he gave the drug he did not get any results. He knew of cases of his that I had cured, and was greatly interested. He pulled out a drawer in his consulting table and said, "I keep a stock of the drug here." He produced cachets of white santonin. Violating the only two conditions I make, viz.: chromosantonin to be given in oil. Second, there is a time in every case when a germicide has its chance. Micro-organisms need time and a breach of surface to invade the tissues and entrench themselves. At first they are on the surface. Entrenching causes destruction of tissue and protects them from the action of the drug. The destruction of tissue may become so great that, even were it possible to kill all the micro-organisms it would not help the patient; or, on the other hand, ill-health may be continued as a result of the complications set up by the implication of other organs. I have had a set of lantern slides made from Dr. WETHERED'S slides that show some of these points very clearly.

In conclusion, I only ask that the properly prepared drug be given a trial in *recent cases*, and I feel convinced that little doubt will be left of its great value. Chronic cases are hardly a fair test, but I venture to hope that the cases Dr. MAXWELL has brought up to-night will go far to influence you.

Sir PATRICK MANSON: I am quite sure of one thing, and that is that Dr. MAXWELL'S paper, backed up as it is by Dr. BEGG'S remarks, will lead to a re-trial of this drug. I will myself renew my experience with chromosantonin, and give it an opportunity with any case of sprue that in future I may come across. Undoubtedly sprue is a very serious disease. I remember very well when Dr. BEGG'S original paper appeared; I confess I was prejudiced against the use of santonin by that very paper. As I understood it, it led one to conclude that he regarded santonin as an effective remedy against sprue because it killed the ascaris lumbricoides, and therefore it would kill the micro-organism,

which he assumed to be the cause of sprue. Seeing that we were in ignorance as to what the nature of that micro-organism was, I did not think this reasoning good. Moreover, I was not satisfied that the cases he described were really cases of sprue. We get many forms of intestinal catarrh associated with diarrhœa, which are readily amenable to doses of castor oil and a little care. These cases I should not call sprue; they may be early stages of the disease or they may not. I think, however, we shall be justified in renewing our trials with the drug. I myself have employed it many times, but unfortunately without good effect. Possibly Dr. Begg has given us the explanation of this failure—my santonin had not been converted into chromosantonin. The next time I try the drug I shall make sure that the necessary change has taken place.

Dr. Carnegie Brown: Although I regret to say that I have not had so fortunate an experience of the results of the treatment of sprue by yellow santonin as Drs. Maxwell and Begg, I have listened to their papers with very great interest, and the Society is much indebted to them for having provided so full a statement of the position, and for having given us a subject so adapted to thoughtful discussion. I think, however, that for many reasons, most of us will feel constrained to question the accuracy of their conclusions. In the first place, let us enquire what is the nature of the transformation which takes place when the admittedly ineffective white santonin is converted into yellow santonin—a remedy for which very special efficacy is alleged. As we all know, santonin turns yellowish-brown on continued exposure to sunlight; and in view of the claims that had been made on behalf of that product, I made a point, some years ago when working at this question, of searching the literature in the Pharmaceutical library, and of consulting several chemists who had investigated the subject as to their views of what was the actual nature of the change. I could find no evidence however in support of Dr. Maxwell's contention that the so-called chromosantonin differs in chemical composition from white santonin. A polariscope reaction does not necessarily imply more than a change of colour, and although there may be some allotropic alteration, the view of pharmacists is that santonin still remains santonin after it has lost certain of its colour constituents by the action of light. Further, we

know that there is no variation in its physiological action, and that santonin, after it becomes yellow, induces xanthopsy and other symptoms in exactly the same way as when it is white. It is, therefore, very difficult to believe that there can exist such a complete difference in the therapeutical virtues of the two forms of the drug.

With regard to the question of history, the use of santonin in sprue dates back for a considerable period. It originated, indeed, in 1876, when the disease was thought by NORMAND and others to be due to the presence of strongyloides stercoralis in the small intestine, and a paper was published in the *Gazette Hebdomadaire* in 1878, by COLIN, a naval medical officer in Cochin China, advocating the general use of the remedy. His advice appears to have been widely followed, but after it was shown by LE BRETON and CHASTAING that the worms had no pathogenic significance santonin passed into disuse, and I have recently heard that in the French Settlements, where, as you know, sprue is so common, further trials have given no satisfactory result.

So far as the success of the treatment of sprue by santonin is concerned, Dr. MAXWELL'S cases appear to me to be anything but convincing. The first case—that of a lady—would at first sight seem to be a strong one, but a certain amount of scepticism is permissible when it is noted that the patient when under treatment was not seen either by Dr. MAXWELL or by Dr. BEGG, and that the statement—which is no doubt what she conscientiously believed—is entirely her own. Nothing is more characteristic of sprue than the almost marvellous change which often takes place when a new drug or treatment of any sort is prescribed. Recently, for instance, I have seen in several cases an apparently miraculous improvement follow the administration of soured milk, but further experience indicates that its practical value as a remedy has, to say the least of it, been absurdly exaggerated. In sprue one must beware of being misled by psychic influences, and they must be carefully excluded from the basis of a scientific argument as to treatment.

I presume that in all of Dr. MAXWELL'S cases the important factor of alcohol was absent, and that the prognosis therefore was exceptionally good. The general physician is seldom fortunate enough to secure such favourable material, and a large number of the relapses after marked improvement which he sees are directly due to the incredulity of his

patient, as to the deleterious effects of whisky and soda. Yet no fact in the treatment of sprue is more clearly proved; and the very best results are attained only when patients are teetotallers.

Finally, I must express my strong conviction that there is and can be no specific remedy for sprue, and that food must always remain the consideration of paramount importance. The results of treatment by special diets are eminently satisfactory, and if carbohydrates are excluded from the dietary, and if other directions are followed, eighty-five per cent. of all sprue patients who come home make a complete recovery with very little assistance from drugs. After a careful trial of yellow santonin and olive oil in some twenty cases, I cannot say that I have ever seen any definite or permanent improvement follow its use, and I do not think it is more efficacious than many other remedies for which similar virtues have been claimed.

Major HARRISON: I should like to ask the writer what is the standard of yellow santonin? And whether rich, golden yellow crystals would be considered sufficiently ripe for use in treatment? I was very much impressed by the results published by Dr. BEGG, and I used santonin of the kind and in the way recommended by him in several cases in India and at home, but I have never obtained the slightest results. It may be my santonin was wrong, but at any rate, it was a rich yellow, and had become so— like Dr. BEGG'S original preparation— by keeping in a dispensary for many years. It occurs to me that possibly we are not dealing with the same disease. It is a surprising thing how frequently we get men home suffering from a diarrhœa which seems to be labelled simply according to the idiosyncrasy of the diagnostician. These are sometimes called sprue, because they have some soreness of the mouth and rather pale motions. Among them I have found cases resembling clinical sprue, from which I obtained a Shiga culture. Then again, you have hill diarrhœa, in which, though the stools are like sprue stools, I do not think is sprue at all. I am inclined to think that the patients of Dr. BEGG and Dr. MAXWELL were not suffering from the same disease as the cases in which other people have tried the drug and failed.

Mr. JAMES CANTLIE: I have tried santonin a good deal, and in fact I may say that in almost every case of intestinal flux, be it due to dysentery, colitis, or sprue, I commence by prescribing santonin. This is, of course, given from the fact that, intestinal parasites are so frequently met with in persons coming from any part of the tropics, that it is well to clear up that point first; so I give either santonin or the mixture of eucalyptus oil, chloroform and castor oil. Santonin possesses this advantage that a short course of it seems to do good, whether a person is ill or not. What the exact action of the drug is I cannot tell; it may have an intoxicating effect, but there is not the least doubt that it induces a feeling of good health. Why it should have any effect on sprue is not clear, nor can I say, that used on the lines which my friend Dr. BEGG has found so successful, have I obtained good results. In fact many people say it makes them feel very bad. Perhaps, however, my santonin has not been sufficiently "yellowed." I agree with Dr. CARNEGIE BROWN that the question has first to be settled: what is sprue? The geographical distribution should also be gone into. I believe sprue was first notified in Sumatra, and travelled northward; Ceylon was the next place it appeared in; and in Southern China it has been known for some time, although I was not aware that sprue had reached the Upper Valley of the Yang-Tse, where Dr. BEGG practised, when I knew China in 1887 to 1897.

Sprue in India seems to have been a recent development; perhaps it was there before but not recognised. At any rate the disease seems to be spreading, and I think the questions of its geographical distribution and diagnosis should be gone into very carefully. One characteristic feature of sprue is the shrinkage of the liver to minute dimensions. Until the liver is stimulated to action I cannot imagine anything is going to do him good. The best thing to do in that case is to knock off the carbo-hydrates, and then stick to a meat diet, in the hope that it will give the liver some work to do.

Dr. BEGG appears to have been very successful with santonin in cases of sprue, but then he practises at Bath, and who would not get well at Bath? I expect, too, the personality of Dr. BEGG, combined with the genial climate of Bath and the good food and olive oil with which he supplies his patients, have, perhaps, more to do with his cures than santonin.

Dr. WILLIAM HARTIGAN: I am afraid I cannot say much on the subject, as I have not used santonin in the treatment of sprue; but I think Dr. CANTLIE's point that santonin of itself has some specific value is a very strong one. I always use it on children suffering from worms, and whether they have worms or not it always has a wonderful effect on the stools, and it has cured several cases of intestinal disorders of various sorts. I think it is very likely that in the experiences of Dr. BEGG and Dr. MAXWELL this drug may have had a very good effect on the patient. It certainly acts on bacteria and stops fermentation.

As regards the difference between chromosantonin and santonin, my recollection is that when I first went to China (1879), the santonin I used was invariably yellow, but in later years the pharmacists supplied it in coloured bottles, so that it was always white. Nevertheless, I found this white santonin just as effective as the yellow.

Again, with regard to the cases brought forward by Dr. BEGG and Dr. MAXWELL, I think they both laid stress on the fact that they have not been successful in chronic cases. In these cases where the liver is small, it is always a sign that shrinking is going on *pari passu* with loss of tone in the intestine and with no digestive power. Carbo-hydrates increase fermentation, and this, together with the weakened digestion, makes the patient worse; therefore the giving up of carbo-hydrates improves the patient. A milk diet soothes the intestines and does not, as a rule, create fermentation. I have seen cases in which santonin was given, and by preventing fermentation it certainly did good. On the other hand there are chronic cases known both to Dr. BEGG and myself in which santonin has been completely ineffective.

Dr. THOMAS RENNIE: My experience of this disease has been small, as I have had very few cases. I begin my treatment, as a rule, with yellow santonin, but I have never found—beyond a general feeling of well-being—that it was of much use in the cure of the disease.

Major S. LYLE CUMMINS said: I should like to give my experience of the use of santonin in a country where there is no sprue. It was in connection with a case of chronic diarrhœa which had lasted for 9 years (not sprue as sprue is generally described). The patient was an Egyptian interpreter in the War Office service. The case came under my obser-

vation in 1904 (the attack being then 8 years old) and I treated the case in hospital for 24 days, but I failed utterly to cure him. In 1905 I saw Dr. Begg's article in the journal of the Royal Army Medical Corps, and I sent for the patient and advised him to come into hospital again. He had not a sore mouth nor an inflamed tongue, but in other respects the condition was closely analogous to sprue. He had diarrhœa which was chiefly confined to the morning; from 5 a.m. till 9 a.m. a very large number of stools, but for the rest of the day it was not so bad—in all about 20 stools a day at the time of admission to hospital. His weight was down to 100 lbs. (originally it had been 135 lbs.) I started off with five grains of santonin twice a day in cachets. It had a most marvellous effect. On the first day of treatment there were 19 stools; on the second day 16; on the third day they had fallen to four and after the third day they became normal. I gave the santonin for a week with milk diet, and at the end of the week put him on ordinary diet.

I may add that the santonin was an old sample yellow in colour, and was exposed to the sun for several days before administration.

Dr. F. M. Sandwith: Dr. Maxwell states in his conclusions that yellow santonin differs completely from santonin as regards its chemical composition. Whether this is so or not, the real point at issue is whether the difference shows itself in physiological action; for instance whether coloration of the urine occurs as rapidly or more rapidly after the administration of yellow santonin than after white santonin. In healthy individuals the well known colour in the urine has been seen as soon as 16 minutes after the administration of the drug, and this is probably irrespective of whether it is given in oil or in cachet. Observations on this point might be made in hospitals on animals as well as human beings.

It must be a source of some satisfaction to Dr. Begg to have assisted at this interesting debate to-night especially when we consider the difficulty he has experienced in getting pharmacologists to consider the question. Professor Cushny in his book published in 1910, says little about yellow santonin, but a fact that ought to encourage Dr. Begg is that in the British Pharmaceutical Codex of 1907 there is a note to the effect that yellow santonin has been recommended for intestinal disorders. I may say that in this note the changed drug is called photo-santonin, which is perhaps a better name than chromosantonin.

It is now nearly 21 years since Dr. Begg called the attention of the profession in Great Britain to the drug in a paper which appeared in the *Edinburgh Medical Journal*. Dr. Begg is certainly optimistic in speaking of the pathology of sprue as if it were a known quantity. If there is anyone who can tell us what the pathology of sprue really is, I am sure the information will be welcome. At present our treatment of the disease is something akin to putting "drugs of which we know little into bodies of which we know less." So far as I am aware, the actual pathology of sprue is quite unknown though we are all familiar with certain appearances in the post mortem room. Mention has been made of a micro-organism but we should like to see it. Dr. Begg, in his Bristol paper, published six years ago, says he found "the layer of mucoid-like material was studded with rod-shaped bodies." It will be interesting to see the lantern slides which Dr. Begg is preparing before offering an opinion. I think it is a question whether "morning diarrhœa" is an early stage of sprue or not. I do think, however, if we are to get to the truth of this question, it will rather be by finding out what sprue is, and not by finding out what santonin can do.

Fleet-Surgeon Bassett-Smith: There is one point which has not been raised this evening, and that is: In cases of sprue we find there is a great abundance of flora in the intestines which keeps up fermentation. I think experiments might be usefully carried out to see whether santonin has any actual effect on this flora. If it did not, it would be difficult to claim that santonin had any specific effect on the disease.

Dr. J. Preston Maxwell: I have to thank you, gentlemen, for your kind remarks. One of the reasons which induced me to write this paper was the fact that so many people have told me that santonin in the treatment of chronic tropical diarrhœa is no good at all. In writing my paper, therefore, I did not deal with the question of failures to any marked extent, as it seemed to me more a matter for us to prove that in some cases at any rate it had a real and lasting effect.

Replying, first, to Dr. Carnegie Brown's expression of doubt as to whether the cases mentioned by me were real sprue, I would like to point out that they have been classed as cases of sprue by eminent

medical men. I admit that the question of what is and what is not sprue is a very open one, and I believe if the Fellows present were asked for their definition of sprue, the answers given would differ a good deal from one another.

With regard to the composition of the drug I think it is now acknowledged that there is a real difference between santonin and chromosantonin. Major HARRISON asked: What is the standard of yellow santonin? I cannot say what should be regarded as a definite standard. One may keep santonin in a bottle in the sun for six months, and even then in the centre of the bottle it would not be converted into chromosantonin. My method of treating santonin in the preparation of chromosantonin is to spread it out in crystals and turn it over from day to day, and I consider the preparation complete when, on crushing a single crystal, you cannot get any large proportion of white colour.

I was asked about the colour of the excretion in the urine. It is difficult to speak on this point, but my experience has been that when using yellow santonin the colour of the urine is deeper.

The Chairman (Sir HAVELOCK CHARLES): Before we close this discussion I should like to move a vote of thanks to Dr. MAXWELL for his interesting paper and the lucid replies he has given to the criticisms made upon it. I think the consensus of opinion as to whether santonin is of value in the treatment of sprue is not very favourable. This may be due to that fact that all medical men are not quite agreed as to what is sprue and also to the fact that santonin has been used by many without it producing any good effect in the treatment of the disease. I think, however, after Dr. MAXWELL'S paper and the discussion which has followed upon it, we shall all be willing to give yellow santonin with olive oil a trial in the treatment of sprue.

ELECTION OF MEMBERS.

The following were duly elected as Fellows of the Society:—

John B. Alexander, M.B., Wick.
Henry Anderson, M.D., Queensland.
Charles T. Andrew, M.B., Chin Wang Tao.
G. W. R. Black, M.D., Hong Kong.
Gabrielle R. S. Breeze, M.B., Tangier.
George Guy Butler, M.B., Lynmouth.
Captain John P. Cameron, I.M.S.
George R. H. Chall, M.R.C.S., Nairobi.
Captain Howard Crossle, I.M.S.
Max des Ligneris, M.D., Transvaal.
John Farrington, M.R.C.S., Fiji.
Major James H. Hugo, I.M.S.
Major Spencer Hunt, I.M.S.
W. Hamilton Jefferys, M.D., Shanghai.
Alexander F. Kennedy, M.B., Coleraine.
F. Markland Longson, M.B., Selangor.
John R. McDill, M.D., Manila.
Ernest E. Maples, M.D., F.R.C.S., Forcados.
Jorge Martinez, M.D., Bogota.
Isaac P. Masters, M.B., Pahang.
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Ralph W. Nauss, M.D., Runcorn.
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Thomas Rennie, M.D., Foochow.

WALTER H. SCOTT, M.R.C.S., Newton Abbot.

JOHN O. SHIRCORE, M.B., Nyasaland.

FRANK STANDISH, M.B., Selangor.

WILLIAM H. T. STORRS, M.R.C.S., Rhodesia.

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FRANK WELLS, M.R.C.S., London.

CHRISTOPHER J. WILSON, M.B., Cobham.

WU LIEN-TEH, M.D., Tientsin.

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